METASTATIC ROUTE ALONG THE PERIPHERAL NERVES THROUGH WHICH MALIGNANT TUMORS MAY REACH THE CENTRAL NERVOUS SYSTEM (EXPERIMENTAL STUDY WITH THE USE OF THE YOSHIDA SARCOMA)

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by

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I INTRODUCTION

The metastasis of a malignant tumor from various parts of the body to the central nervous system (parenchyma of the brain and spinal cord or the meninges) appears in one of the following types;

1) node-forming type in the parenchyma of the brain and the spinal cord,
2) diffuse-infiltrating type in the leptomeninges,
3) node-forming type in the dura or in the epidural and subdural spaces.

Metastasis of node-forming type in the parenchyma of the brain and spinal cord is believed to be due to a hematogeneous dissemination of tumor cells to the central nervous system.

As to the second type of metastasis, i. e., the diffuse-infiltrating type in the leptomeninges, some assume a hematogeneous spreading and others postulate a lymphogeneous metastasis along the peripheral nerves, but both of these assumptions seem to lack the definite experimental basis.

About the node-forming type of the metastasis in the dura or in the epidural or subdural spaces, possibilities of the hematogeneous, lymphogeneous or continuous spreading of tumor cells have been discussed by many investigators.

However, according to KIHARA[35], in the central and peripheral nervous system, a lymph duct is observable neither in the parenchyma nor in its covering. Thus, the lymphogeneous metastasis of malignant tumors into the central nervous system can be excluded.

Regarding the continuous metastasis, it is presumed that the intra- and extra-neural tissue spaces of the peripheral nerve would play an important role.

In the present experimentation, the author tried to investigate the metastatic routes of malignant tumor to the central nervous system other than the hematogeneous route.

Ⅱ MATERIALS AND METHODS

Experimental animals used, were hybrid rats weighing about 70-130 gm. India-ink suspension in the physiological saline solution* and the suspension of the Yoshida sarcoma cells in the physiological saline solution** were prepared for the injection and inoculation to the animals.

EXPERIMENT 1. India-ink injection into the subarachnoid space of the cranial cavity: With a suboccipital puncture, the rats were injected with 0.05-0.1 cc of India-ink into the subarachnoid space very slowly. These rats were sacrificed about 10-20 minutes after the injection, and immediately fixed by an intraveneous infusion of the 10% formalin solution. The diffusion or distribution of India-ink in the subarachnoid space was examined macroscopically with the aid of a magnifying glass. Then the cranium and vertebra with surrounding soft tissues were decalcified and embedded in toto in celloidin. Serial sections of 10-20 microns thickness were made, and chiefly stained with hematoxylin and eosin for the microscopic examination.

EXPERIMENT 2-a. India-ink injection into the surrounding tissue of the intraorbital optic nerve: With a curved needle, 0.05-0.1 cc of India-ink was injected into the surrounding of the optic nerve behind the right eye ball through the conjunctival sac. Animals were sacrificed 10 minutes to 24 hours after the injection, and examined in the same way as in EXPERIMENT 1.

EXPERIMENT 2-b. India-ink injection into the surrounding tissue of the sciatic nerve trunk: In rats right major psoas muscle was exposed transperitoneally, and 0.1-0.2 cc of India-ink was injected into the surrounding of the right sciatic nerve trunk by puncture through the same muscle at the level of the Ⅰ-Ⅳ sacral vertebra. The rats were sacrificed 10-20 minutes after the injection, and were fixed and studied in the same way as in EXPERIMENT 1.

EXPERIMENT 3. Inoculation of the Yoshida sarcoma into the subarachnoid space of the cranial cavity: The suspension of Yoshida sarcoma, 0.05-0.1 cc, was inoculated into the subarachnoid space of the cranium through a suboccipital puncture (in the same procedure as in EXPERIMENT 1). The rats were sacrificed or let die naturally after various periods of interval, and studied in the same manner as in the foregoing experiments.

EXPERIMENT 4-a. Inoculation of the Yoshida sarcoma into the surrounding tissue of the intraorbital optic nerve:

EXPERIMENT 4-b. Inoculation of the Yoshida sarcoma into the surrounding tissue of the sciatic nerve trunk:

Both procedures were carried out in the same way as in EXPERIMENT 2-a and 2-b, using 0.05-0.1 cc of the suspension of Yoshida sarocoma. The experimental rats were sacrificed or let die naturally at various intervals after the the transplantation, then studied macroscopically and microscopically in the same

* hereafter will be used an abbreviation "India-ink".

** 5-10× dilution of Yoshida sarcoma ascites with physiological saline solution; hereafter will be used an abbreviation "suspension of Yoshida sarcoma".

way as in EXPERIMENT 3.

Ⅲ RESULTS

EXPERIMENT 1. India-ink injection into the subarachnoid space of the cranial cavity:

Macroscopic findings: Autopsy revealed that India-ink had spread out throughout the subarachnoid space and in all of the ventricles. Surface of the brain and spinal cord, wall of the ventricles and the central canal were diffusely stained in black. On the surface of the brain and spinal cord, this black staining was most remarkably seen at the cranial and spinal nerve roots, around the blood vessels and along the cerebral fissures and sulci. The olfactory and the optic nerve were discolored in black along their entire course from the base of the brain to the peripheral end, while the other cranial and spinal nerves were stained only at their roots. Lymph ducts starting from the subcutanous tissue at the medial canthus and the supramaxilla and running along the v. facialis anterior were demonstrated as black cords. Lymphonodi submaxillares and lymphonodi cervicales superficiales et profundi were also stained with dye.

Microscopic observations: India-ink particles which had been diffused throughout the subarachnoid space, precipitated in the pia mater and the arachnoid. These India-ink particles were most abundantly observed in regions where the macroscopic discolorations were most prominent. In the parenchyma of the brain and spinal cord, India-ink particles were deposited in the VIRCHOW-ROBIN's space. The olfactory nerve was surrounded with India-ink along its entire course, from the base of the brain to the submucous tissue of the nose. The optic nerve contained the India-ink particles in its spatium intervaginale and inside of its vagina interna (Figs. 1, 2). Other cranial nerves contained no India-ink particles inside of the perineurium. At the spinal level, India-ink was streamed away from the subaranchnoid to the outside of the spinal cavity along the anterior and posterior roots or through the interior of the spinal nerves (Fig. 3).

EXPERIMENT 2-a. India-ink injection into the surrounding tissue of the intraorbital optic nerve:

Macroscopically, the corpus adiposium orbitae, eye muscles, lacrimal glands and a part of sclera were diffusely stained with India-ink, but it was not the case either on the cut surface of the optic nerve or in the cranial cavity. In the subcutaneous tissue of the face and neck, the lymph ducts and the lymph nodes were discolored in black just as seen in EXPERIMENT 1. Microscopically India-ink particles were found neither inside of the vagina fasciculi opitici nor in the parenchyma of the optic nerve, even in regions where the optic nerve was in direct contact with the surrounding India-ink imbibition. Penetration of India-ink toward the intracranial cavity or into the eye ball along the optic nerve was not observed.

EXPERIMENT 2-b. India-ink injection into the surrounding tissue of the sciatic nerve trunk:

Macroscopically, a relatively localized black discoloration was seen around the

point of injection in the major psoas muscle, from which black lines extended cranially and caudally along the lumbar and sacral nerves for few milimeters. Occasionally, these black lines could be followed up to the outside of the intervertebral foramen. With microscopical studies, it was found that few India-ink particles which had suurrounded these lumbar and sacral nerves, adhered to the outer surface of the perineurium, but they were never present inside of the perineurium. Also India-ink particles were not found in the spinal cavity and in the intervertebral foramen.

EXPERIMENT 3. Inoculation of the YOSHIDA sarcoma into the subarachnoid space of the cranial cavity:

Usually from the third day on after inoculation animals became inactive and anorectic, and began to secrete a serous-hemorrhagic fluid from the conjunctiva and the nasal mucous membrane. Further, emaciation and general weakness developed, and death usually occurred on the 6th day after the transplantation. Some cases showed ataxia or increased irritability before the death.

Macroscopically, a loose adhesion between the skull and the pachymeninx, and a somewhat edematous appearance of the leptomeninx were the only findings. No abnormal findings were noticeable in the spinal cavity and in the peripheral nerves. Metastasis of sarcoma was observed only in the submaxillar lymph nodes, and no ascites was found in the abdominal cavity.

Microscopic observation: Numerous cells of the YOSHIDA saroma were always found in the smear preparations taken from the cranial and spinal cavity (GIEMSA stain). Throughout the subarachnoid space of the cranium, especially at the base of the brain, it was filled with the YOSHIDA sarcoma cells (Fig. 4), while there were found relatively few sarcoma cells in the ventricles and in the subarachnoid space of the spinal cord (Fig. 7). Hydrocephalus was not observed. Tumor cells invaded under the epithelium of the plexus chorioideus and also into the VIRCHOW-ROBIN'S space (Figs. 5, 6). Occasionally they infiltrated into the subdural and epidural spaces, or even into the bone marrow of the skull. Generally, the sarcoma cells in the subarachnoid space flowed out to the periphery along the cranial and spinal nerves much more easily and abundantly than India-ink, although there was no essential difference in the way of spreading between the two. The spatium intervaginale of the optic nerve was filled with the sarcoma cells along its entire course, but no tumor infiltration was observed in the parenchyma of the optic nerve (Fig. 8). The olfactory nerve was also surrounded with sarcoma cells along its entire course. As to the other cranial nerves, sarcoma cells flowed out from the cranial subarachnoid space along each nerve root (outside of the perineurium), or through the interior of the nerve root (inside of the perineurium), but they never extended outward to the peripheral ends (Fig. 9). Sarcoma cells which had appeared in the vertebral canal, after infiltrating along the dura or arachnoid around the nerve roots, or into the nerve parenchyma or spinal ganglions, further flowed out from the vertebral canal. In no case, however, there were found sarcoma cells spreading further beyond the intervertebral foramen (Fig. 10).

EXPERIMENT 4-a. Inoculation of the YOSHIDA sarcoma into the surrounding

tissue of the optic nerve in the orbit:

From about the 3rd day on after transplantation, the experimental rats began to show exophthalmus, epiphora and muddiness of the cornea. These symptoms developed increasingly and the animals died on an average on the 9th day as the result of emaciation. By necropsy, a relatively localized tumor of rice to soy-bean size was found in the orbit behind the eye ball. No pathological findings was observed in the cranial cavity macroscopically. Metastases were found in the lymphonodi submaxillares et cervicales.

Microscopically the tumors in the orbit enveloped the optic nerve and showed a histological picture of so-called "subcutaneous tumor of Yoshida sarcoma". Growth of the tumor was principally of expansive type, and the tumor was limited by the side wall of the nasal cavity ventrally, and by the cranial basis near the choana posteriorly. The optic nerve in the orbit was surrounded by the sarcoma cells. The vagina fasciculi optici was scarcely infiltrated with the sarcoma cells, but occasionally tumor cells appeared in the spatium intervaginale perforating the vagina externa (Fig. 13). The parenchyma of the optic nerve was not infiltrated with the sarcoma cells. Tumor cell infiltration in the orbit reached right the outside of the optic foramen along the optic nerve, but did not further extend into the optic foramen. Therefore, infiltration of the sarcoma cells into the cranial cavity through the optic foramen was never observed. On the other hand, the sarcoma cells extending extracranially to the cranial basis from the orbit, infiltrated into the pterygopalatine fossa, and occasionally invaded into the bone marrow of the base of the skull or even into the intracranial cavity. In these cases, the sarcoma cells infiltrated into the pacymeninges, forming a localized flat tumor in the epi- and subdural spaces. The sarcoma cells, however, had invaded neither into the subarachnoid space nor into the parenchyma of the brain (Figs. 11, 12).

EXPERIMENT 4-b. Inoculation of the Yoshida sarcoma into the surrounding tissue of the sciatic nerve trunk:

The tumor growing behind the major psoas muscle increased in size day by day, and finally came to surround the vertebra in its half circumference. The experimental rats generally died on an average on the 13th day after transplantation. Ascites was not observed in any case.

Microscopically a relatively localized area of sarcoma cell infiltretion was observed in the major psoas muscle from which tumor cells extended towards the intervertebral formen along the lumbar and sacral nerves. In the early stage, the sarcoma cells invaded inward through the intervertebral foramen, and enveloped the spinal nerve and the spinal ganglion (Fig. 14). Later, on the other hand, tumor cells plugged the intervertebral foramen, penetrated into the spinal nerve and spinal ganglion, or further infiltrated continuously from the intervertebral foramen into the epidural space of the vertebral canal (Fig. 15). These sarcoma cells in the epidural space occasionally infiltrated into the dura mater, but not into the arachnoid membrane. Consequently, the sarcoma cells were not observed inside of the arachnoid at all (Figs. 16, 17). [Only in one exceptional case, sarcoma cells infiltrating into the cauda equina was observed (Fig. 18).] In the lastest stage,

the bone marrow of the vertebra was replaced with sarcoma cells.

Ⅳ DISCUSSION

The fate of a dye which had been injected into the subarachnoid space were investigated in detail by DOLDMANN[19] FUKUCHI[17] KOYAMA[42] KIHARA and co-workers [21),35),36),60),70] They described that a dye flowed out from the subarachnoid space to the periphery, infiltrating into the capsules or surrounding tissues of the nerve roots. It had been also reported that a dye in the subarachnoid space was absorbed into the venous sinus through the arachnoid villi or directly into the veins on the surface of the brain[5),17]

In the present investigation, it was proved that the India-ink injected in the subarachnoid space, flowed out to the periphery diffusing along the out- and inside of the nerve roots, and through the out-and inside of the spinal ganglion and the spinal nerves.

On the other hand, YOKOGAWA[95] reported that the India-ink which had been injected into the nasal submucous tissue had moved into the subarachnoid space in the cranial cavity. ISAYAMA[31] reported that the India-ink injected in the eye ball (vitreous body), did not appear in the parenchyma of the optic nerve.

In the present investigation, the India-ink which had been injected into the surrouding of the optic nerve and of the sciatic nerve trunk did not appear in the parenchyma of the nerves (inside of the perineurium) and in the subarachnoid space of the central nervous system.

According to the experiments in the literature on the transplantation of a malignant tumor into the brain tissue, tumor cells frequently infiltrate into the meninges as well as into the parenchyma of the brain, i. e.. so-called meningeal carcinomatosis or sarcomatosis may develop.

In the present investigation, the meningeal sarcomatosis was experimentally produced by the inoculation of the YOSHIDA sarcoma into the subarachnoid space. And this was confirmed by histological findings such as tumor cell infiltration into the meninges, in the VIRCHOW-ROBIN's space and in the plexus chorioideus without a vigorous interstitial reaction.

Experimental studies concerning the mode of the infiltration of the transplanted tumor cells in the peripheral nerves, in the cranial and spinal cavity, have been carried out only in the field of the ophthalmology or oto-rhino-pharyngo-laryngology. HOSODA[21] TAKEUCHI[82] described that the experimental tumor of the auditory organ had infiltreted into the epidural space and pachymeninges of the cranium chiefly through the destructed skull and partly along the nerve roots, and that these invasive tumors had only compressed the brain from the outside. Clinically, it was reported that the cancer of the paranasal sinus[6),61] that of the face[49] and the malignant tumor of the parotid gland[63] had invaded into the cranial cavity destroying the skull or infiltrating along the nerve roots or the blood vessels and further into the meninges and the brain tissue. KNIERIM[31] and others[2),25),34),45),48),54),66),83] stated that the tumor cell infiltration around the spinal nerve plexus or around the

spinal nerve trunk proceeded into the spinal cavity to result in a diffuse meningeal carcinomatosis or sarcomatosis. On the other hand, BERTHA[10] and BUERGSTEIN[12] were of the opinion that those tumor cells could invade into the parenchyma of the peripheral nerves and pachymeninges of the spinal cord, but could not invade into the subarachnoid space because of 1) the biological defens mechanism of the leptomeninges and 2) the stream of the cerebrospinal fluid.

In the present study, the YOSHIDA sarcoma cells which had been inoculated into the surrounding of the peripheral nerve trunk did only invade into the epidural and subdural spaces, passing through the intervertebral foramen or after destroying the cranial basis in the late stage, but did not infiltrate into the subarachnoid space or into the parenchyma of the brain or spinal cord. These results may suggest that it is hardly possible that the tumor cells metastasize from an extracranial or extravertebral tissue into the cranial or spinal cavity (in the subarrachnoid space and in the parenchyma of the brain and spinal cord) via the continuous ascending routes.

V SUMMARY AND CONCLUSION

1. India-ink which had been injected into the subarachnoid space rapidly diffused throughout the subarachnoid space, and flowed out to the periphery mainly through the outside and sometimes also through the inside of the cranial and spinal nerve roots.

2. India-ink which had been injected into the surrounding of the intraorbital optic nerve and the sciatic nerve trunk did infiltrate neither into the parenchyma of the nerves, nor into the cranial and spinal cavities.

3. By the transplantation of the YOSHIDA sarcoma into the subarachnoid space, so-called diffuse meningeal sarcomatosis was experimentally produced. These tumor cells in the subarachnoid space flowed out to the periphery along the outside and sometimes also inside of the cranial and spinal nerves roots.

4. The YOSHIDA sarcoma which had been inoculated into the surrounding of the intraobital optic nerve could not pass beyond the optic foramen inwards into the cranial cavity. Tumor cells occasionally infiltrated into the pachymeninges through the destroyed bone at the base of the cranium, but could not infiltrate into the subarachnoid space or into the brain tissue.

5. The YOSHIDA sarcoma which had been inoculated into the surrounding of the sciatic nerve trunk extended to the intervertebral formen along the nerve trunk, further invaded into the parenchyma of the nerve trunk or into the epi- and subdural spaces of the spinal canal, but did not infiltrate into the inside of the arachnoid membrane.

6. As a general rule, the YOSHIDA sarcoma, which infiltrated into the cranial and spinal cavities after destroying the skull or through the intervertebral foramen, ceased its progress at the pachymeninges, and did not invade into the subarachnoid space or into the central nervous tissue.

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ABBREVIATIONS IN FIGURES:

B: Bulbus oculi
BC: Base of cranium
Br: Brain tissue
Ch: Chorioidea
F: Fasciculus opticus
G: Spinal Ganglion
I: India-ink particles
PN: Peripheral nerve
Pno: Papilla nervi optici
R: Nerve root
S: Sarcoma cell infiltration
SN: Spinal nerve
Sp: Spinal cord
V: Vertebra

EXPLANATION OF THE FIGURES:

Fig. 1. India-ink was injected into the subarachnoid space. Peripheral part of the optic nerve contains the India-ink particles in its spatium intervaginale. ×56

Fig. 2. Ditto. Section of the papilla nervi optici. ×130

Fig. 3. Ditto. Cervical region of the spinal cord. ×56 India-ink particles are most abundantly seen around the nerve root, flowing out to the periphery along the out-and inside of the nerve roots.

Fig. 4. The Yoshida sarcoma transplantation into the subarachnoid space. The subarachnoid space and Virchow-Robin's space are filled with Yoshida sarcoma cells. ×56

Fig. 5. Ditto. Sarcoma cells infiltrate under the epithelium of the plexus chorioideus. ×56

Fig. 6. Ditto. Cervical region of the spinal cord. Sarcoma cells invading into the Virchow-Robin's space. ×330

Fig. 7. Ditto. Cervical region of the spinal cord. Sarcoma cells floating in the canalis centralis. ×330

Fig. 8. Ditto. Sarcoma cells infiltrating outward to the periphery along the optic nerve. ×56

Fig. 9. Ditto. Sarcoma cells in the subarachnoid space are seen escaping to the outside of the cranium along the cranial nerve (n. vagus). ×56

Fig.10. Ditto. Sarcoma cells in the subarachnoid space invading nerve roots, spinal ganglion and spinal nerve. (Cervical region of the spinal cord) ×56

Fig.11. The Yoshida sarcoma transplantation into the surrounding of the intraorbital optic nerve. Sarcoma cells outside of the cranial basis invade into the epidural space of the cranium destroying the skull. ×56

Fig.12. Ditto. Localized sarcoma cell infiltration in the epidural space (base of cranium). ×56

Fig.13. Ditto. The optic nerve being surrounded by sarcoma cells. Sarcoma cells are also seen in the spatium intervaginale. ×150

FIGURES (1)

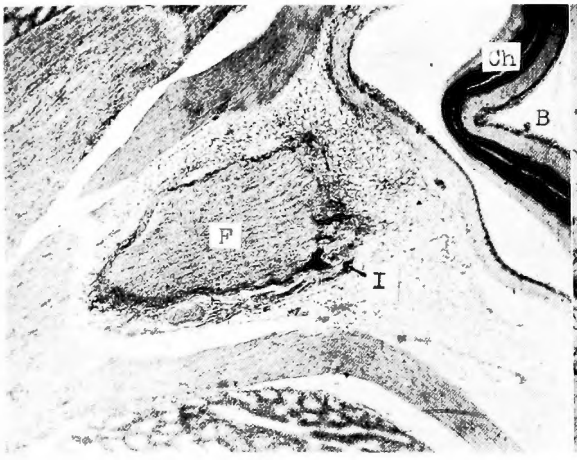

Fig. 1

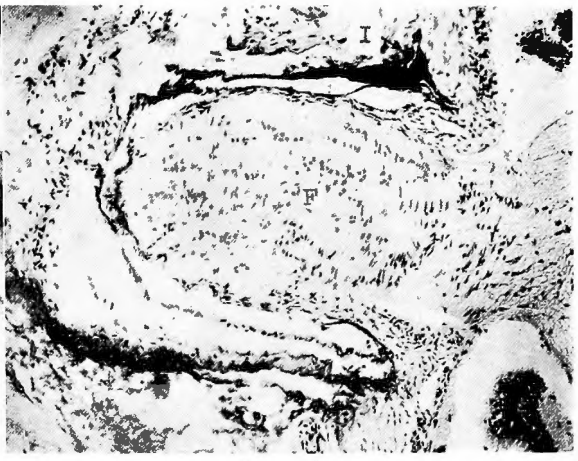

Fig. 2

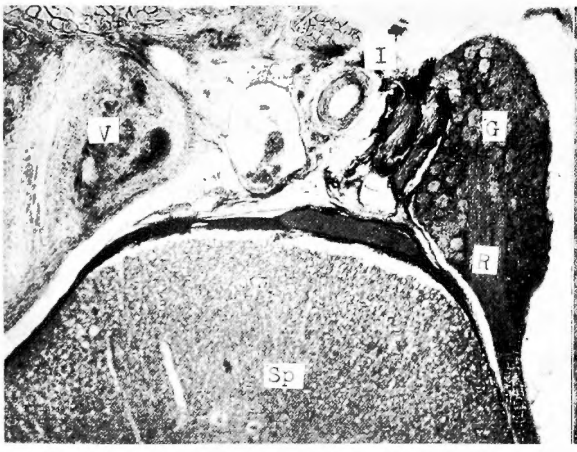

Fig. 3

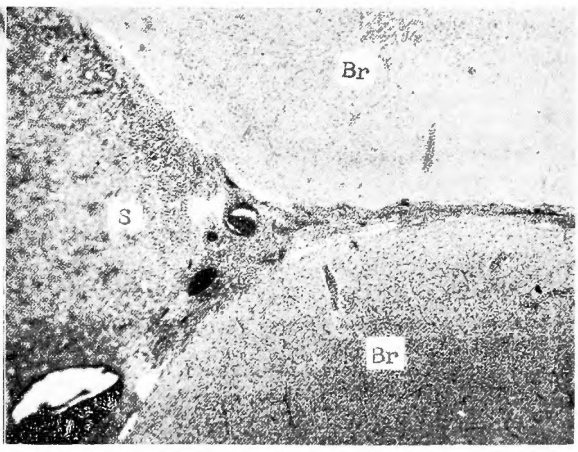

Fig. 4

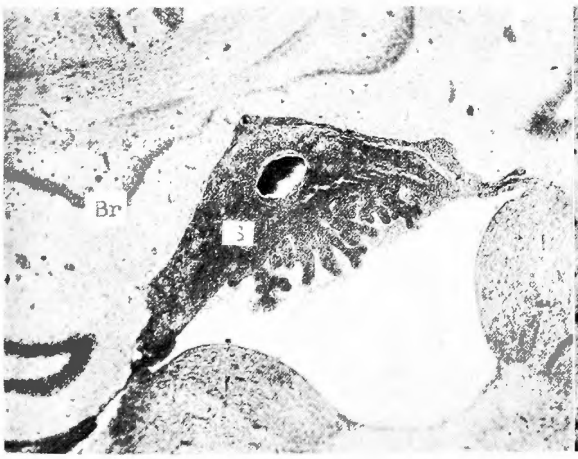

Fig. 5

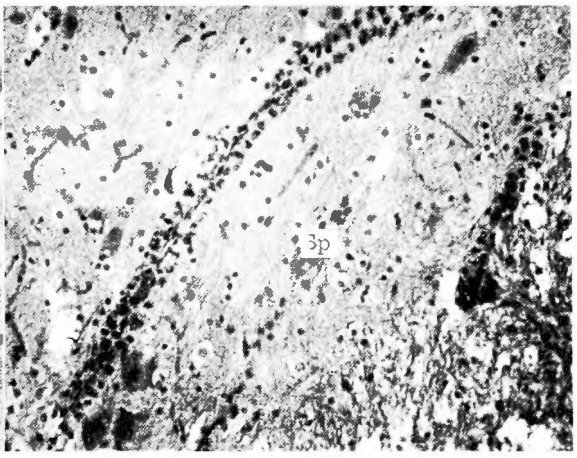

Fig. 6

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FIGURES (2)

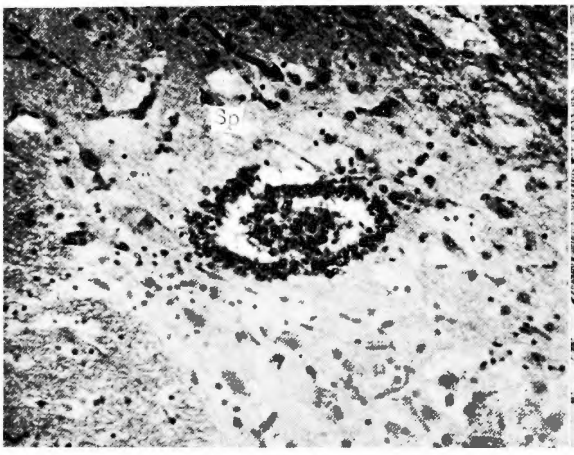

Fig. 7

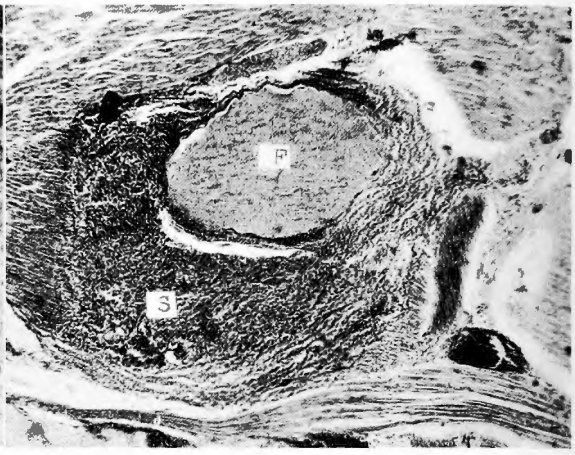

Fig. 8

Fig. 9

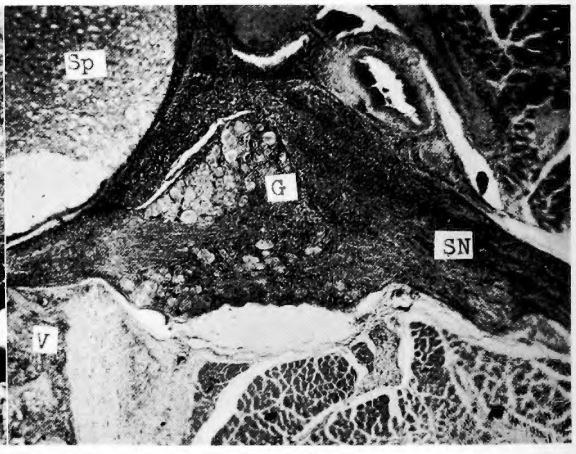

Fig. 10

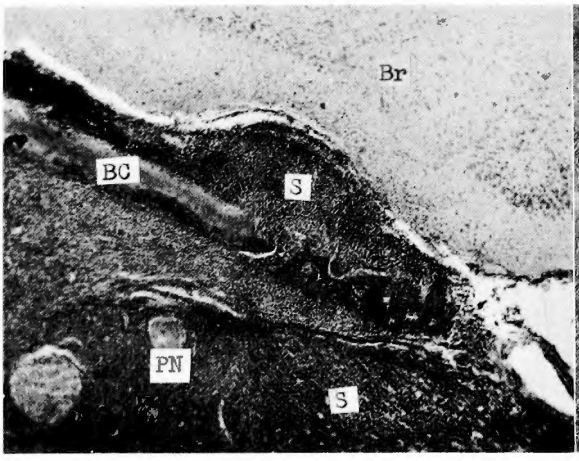

Fig. 11

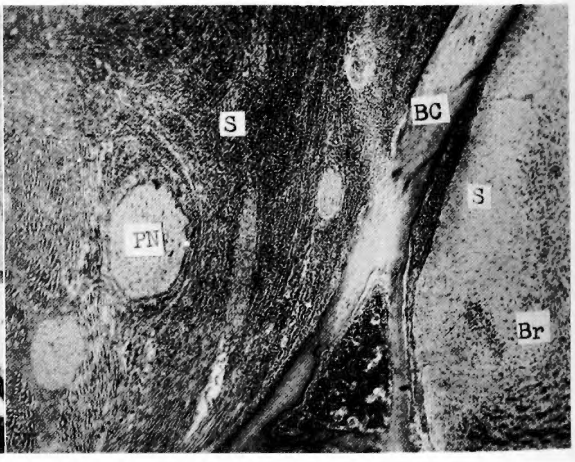

Fig. 12

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FIGURES (3)

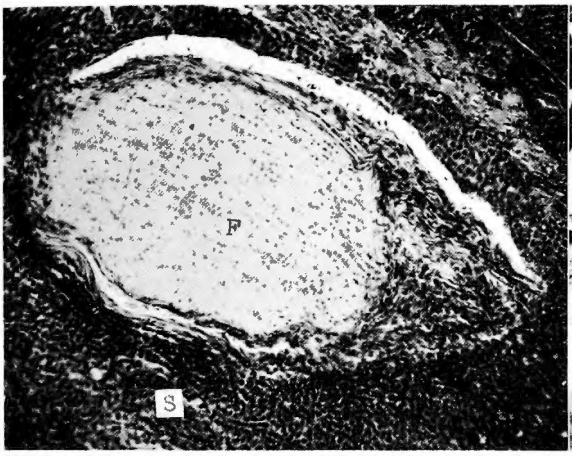
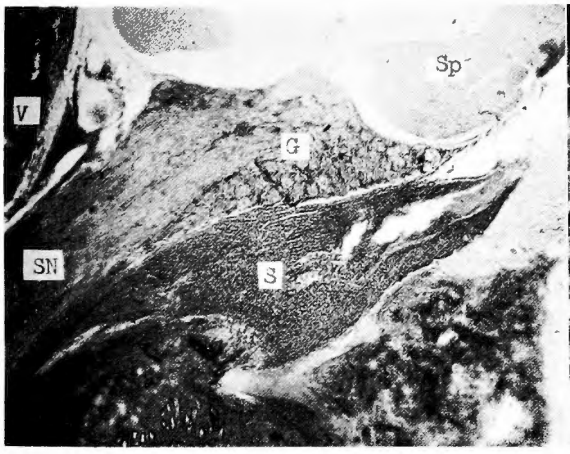


Fig. 13

Fig. 14



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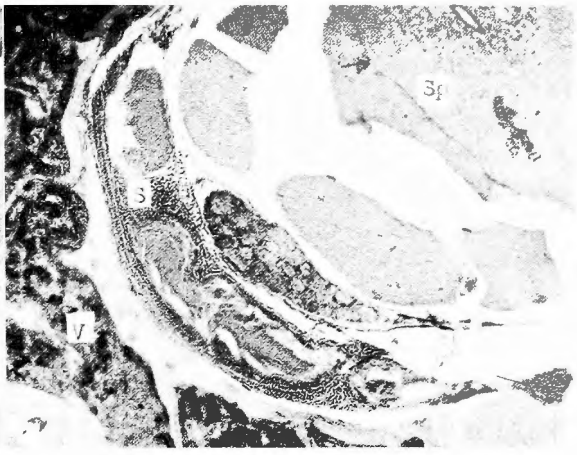

Fig. 16

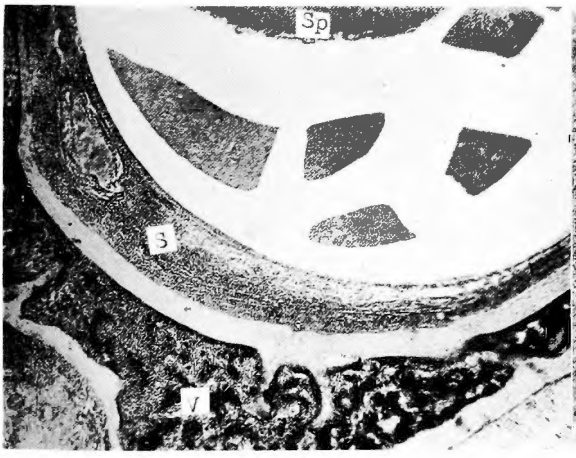

Fig. 17

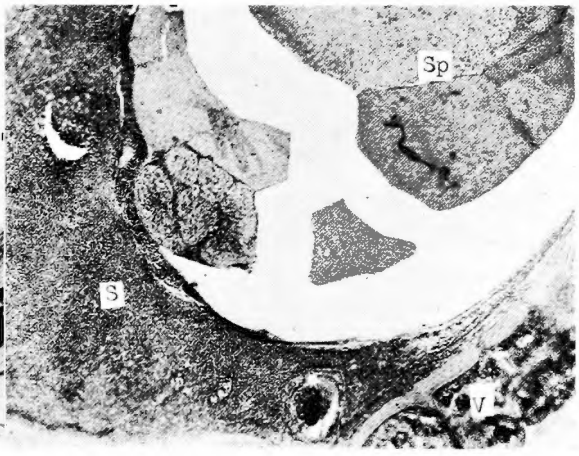

Fig. 18

N. ITO

Fig.14. The YOSHIDA sarcoma transplantation into the surrounding of the sciatic nerve trunk. Sarcoma cells infiltration into the intervertebral foramen along the lumbar nerve trunk. ×56
Fig.15. Ditto. ×56
Fig.16. Ditto. (lumbar vertebra) Sarcoma cell infiltration in the epidural space. ×56
Fig.17. Ditto. ×56
Fig.18. Ditto. Sarcoma cells in the epidural space exceptionally infiltrate into the pachy-and leptomeninges, further into the cauda equina. ×56

和文抄録

末梢神経幹を上行して脳脊髄に達する悪性腫瘍転移経路

(吉田肉腫移植による実験)

京都大学医学部外科学教室第1講座 (指導 荒木千里教授)
国立京都病院外科 (院長 萩原義雄博士)
伊藤直樹

中枢神経系内(頭蓋,脊椎管内)への悪性腫瘍転移形成の様式には,(1)脳脊髄実質内腫瘤形成型,(2)瀰漫性軟膜浸潤型及び(3)硬膜外,硬膜下腫瘤形成型の3型がある.これらの転移経路として血行性,リンパ行性及び連続性伝播経路が考えられている.著者は大黒鼠の中枢神経系内及び末梢神経幹周囲に墨汁及び吉田肉腫を注入,接種し,これら血行性以外の転移経路について実験的に次の結論を得た.

1) 軟膜腔に注入された墨粒は速かに腔内に拡散し,脳脊髄神経根部よりその周囲又は神経被膜下を通路として末梢側に流出する.

2) 眼窩内視束及び坐骨神経幹の周囲に注入された墨粒は該神経質内及び脳脊髄脳内へは移行しない.

3) 軟膜腔に吉田肉腫細胞を移植し,いわゆる瀰漫性脳膜肉腫症を実験的に作製し得た.この軟膜脳内の吉田肉腫細胞は脳脊髄神経根部の周囲に沼い,又は神経繊維間を通路として末梢側へ流れをなして侵出し,嗅糸,視束ではその末梢端まで達するが,脊髄では椎間孔より外へは出ない.

4) 視束周囲に移植された吉田肉腫は視束管を内方に向つて通過し得ない.この肉腫細胞浸潤は脳底部より骨を侵し硬膜に浸潤を及ぼすことがある.しかし硬膜腔,脳実質には浸潤しない.

5) 坐骨神経幹周囲に移植された吉田肉腫は神経幹の外側にそつて椎間孔より神経幹実質及び脊椎管内硬膜内外に侵入するが,蜘網膜より内部には浸潤しない.

6) 上行性に骨を破壊して,或いは椎間孔より頭蓋腔内,脊椎管内に浸潤した肉腫は硬膜までで進行を停止し,軟膜腔,脳脊髄実質中へは侵入し得ないのを原則とする.